Remarks

Claims 38-44, 46-87, and 90-92 were pending in the subject application. By this Amendment, claims 67-73 have been cancelled. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicant's agreement with or acquiescence in the Examiner's position. Accordingly, claims 38-44, 46-66, 74-87, and 90-92 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application. Also submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicant respectfully requests that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

Claims 38-44, 46-87, and 90-92 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description, and as constituting new matter. The applicant respectfully traverses and submits that the subject specification provides a sufficient written description of the claimed invention. Furthermore, the claimed subject matter does not represent new matter.

New Matter

At page 5, the Office Action notes that the specification "makes no mention of interfering RNA." This is not determinative of whether the claimed subject matter represents new matter. The applicant submits that the subject specification, taken as a whole, would lead one of ordinary skill in the art to use RNAi molecules that interfere with expression of SHIP-1 mRNA. For example, the Examiner's attention is directed to the following portions of the subject application: page 5, lines 1-24; page 7, lines 13-29; page 8, lines 3-4, 11-12, 17-19, and 21-25; page 9, lines 10-15; page 11, lines 8-9; page 12, lines 13-18; page 13, lines 23-24; and claims 1-5 of the application as originally filed. The Examiner must consider the common usage of the term "interfering" at the time the subject application was filed, which was after the advent of RNAi. For the sake of clarity of the

record, the applicant respectfully requests that the Examiner indicate whether the Examiner is taking official notice of the common usage of the term "interfering" in connection with transcription and/or translation of a target gene's RNA at the time the application was filed, within the meaning of 37 C.F.R. §1.104(d)(2); MPEP §2144.03. The applicant respectfully submits that the subject specification sets forth sufficient "blaze marks", as required in *In re Ruschig*, 379 F.2d 990; 154 USPQ 118 (CCPA 1967), to lead one of ordinary skill in the art to interfering RNA. Assuming *arguendo* that the term "means for interfering with transcription and/or translation of SHIP RNA" encompasses a genus of various inhibitors, interfering RNA would be singled out and immediately envisioned by one of ordinary skill in the art, based on the teachings of the subject specification as a whole.

The subject specification teaches that the inhibitor of SHIP-1 function can be a genetic construct, such as "an anti-sense oligonucleotide, an RNA aptamer capable of inhibiting SHIP enzymatic activity, an RNA aptamer capable of inhibiting a ribozyme, or another genetic construct of inhibiting SHIP activity known to those of skill in the art" (page 11, lines 10-15). The specification teaches that the substance that inhibits SHIP function can be a nucleic acid that hybridizes to a SHIP mRNA (page 5, lines 33-34; page 6, lines 26-27; and page 11, lines 25-26). The specification teaches that the delivered nucleic acid molecule can incorporate into a specified gene so as to inactivate the gene and "turn off" the product the gene was making, or to alter the translation or stability of the mRNA of the specified gene product (page 12, lines 13-16). The subject application teaches that the nucleic acid can be either RNA or DNA, may be a non-coding sequence, and may be single-stranded or double-stranded (page 14, lines 7-9 and 15). Furthermore, the specification teaches that the SHIP inhibitor can be DNA that directs production of RNA or a polypeptide that inhibits SHIP function (page 15, lines 33-34). There is no requirement that any one segment of the specification, standing alone, has to provide the full support for the claims. Rather, the assessment is to be made from the perspective of one of ordinary skill in the art at the time the application was filed, guided by the teachings of the specification as a whole. Based on the characteristics provided in the subject specification, one of ordinary skill in the art would immediately envision interfering RNA as a means for inhibiting translation of SHIP-1 at the time the application was filed.

Finally, the applicant notes that claims 74-87 and claims 90-92 do not recite the term "interfering RNA" and find support in those portions of the specification set forth in the Amendments in which those claims were introduced.

Written Description

At page 3 of the Office Action, it is acknowledged that the specification provides an adequate written description of the target SHIP-1 molecules recited in the claims. However, at page 4, the Examiner indicates that the specification and claims do not adequately describe the concise structural features that distinguish structures within the claimed genus from those without (*e.g.*, the nucleotide sequences or a representative number of RNAi molecules of the generic RNAi structures claimed, which specifically bind and inhibit SHIP-1 function *in vivo*, and which suppress graft-versus-host disease and transplant rejection).

The test for determining whether a claimed invention is adequately described in the specification is whether the originally filed disclosure reasonably conveys to a person of ordinary skill in the art that the applicant had possession of the subject matter claimed. As acknowledged in the Office Action, the specification provides an adequate written description of the target SHIP-1 mRNA recited in the claims. Having the sequence of the target gene (SHIP-1) and knowledge of its structure, including its relevant isoforms, at the time of filing, one skilled in the art could readily envision target nucleic acid sequences within and along the recipient mammal's mRNA. Furthermore, nucleic acid molecules likely to hybridize with SHIP-1 mRNA and interfere with its expression could then be determined. Due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. The following publications were previously made of record: International Publication WO 99/32619 (Fire *et al.*), Tuschl T. *et al.* (*Genes & Development*, 1999, 13:3191-3197); Zamore P. *et al.* (*Cell*, 2000, 101:25-33); Svoboda P. *et al.* (*Development*, 2000, 127:4147-4156); Tuschl, T. *et al.* (*Chembiochem*, 2001, 2(4):239-245); Elbashir S. *et al.* I (*Nature*, 2001, 411:494-498); Elbashir S. *et al.* II (*Genes & Development*, 2001, 15:188-200) and Caplen N.J. *et al.* (*PNAS*, 2001, 98(17):9742-9747). RNAi is triggered by dsRNA and results in sequence-specific degradation of homologous single-stranded target RNAs. When dsRNA containing a sequence complementary to a specific mRNA target is

administered to cells, it is processed into short nucleotide fragments that guide the cleavage of the transcript. Thus, the endogenous mediators of RNAi are short (*e.g.*, 21-23-nucleotide) interfering RNAs (siRNAs) generated from the longer double-stranded RNAs by the ribonuclease III activity of the highly conserved dicer enzyme (Tuschl T. *et al.* (1999); Zamore P. *et al.*; Elbashir S. *et al.* I; and Elbashir S. *et al.* II). It has been demonstrated that RNAi-mediated gene suppression can be obtained in mammalian cells by delivery of chemically synthesized short (*e.g.*, less than 30 nucleotides) double-stranded siRNA molecules or by endogenous expression of short hairpin RNAs (shRNAs) bearing a fold-back stem-loop structure (Elbashir *et al.* I).

The interfering RNA and hybridizing nucleic acid molecules recited in the claims are not described by function alone. As is evidenced by the aforementioned publications, structural attributes of interfering RNA, including size and content, were known in the art at the time the application was filed (see, for example, pages 197-198 of Elbashir S. *et al.* II). Elbashir *et al.* proposed directly introducing short (*e.g.*, 21-23 nucleotides) dsRNA (siRNA) into mouse and human cells to avoid the problems associated with the expression of longer dsRNAs (Elbashir S. *et al.* I). Elbashir *et al.* state:

> The finding that synthetic 21- and 22-nt siRNA duplexes can be used for efficient mRNA degradation demonstrates that the targeting step can be uncoupled from the dsRNA-processing step. This raises the prospects of using siRNA duplexes as new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNA may be effective in mammalian systems, where long dsRNAs cannot be used because they activate the dsRNA-dependent protein kinase (PKR) response (Clemens 1997). As such, the siRNA duplexes may represent a new alternative to antisense or ribozyme therapeutics. (Elbashir S. *et al.* II, page 198, column 2)

Hence, having the nucleotide sequence of the target gene provides discerning information regarding the sequences (*i.e.*, structural information) of suitable interfering nucleic acid molecules, and leads one of ordinary skill in the art to their selection. Accordingly, the teaching of the subject specification and knowledge of the sequence and structure of the SHIP-1 gene provides sufficient structural and functional correlates to describe the genus of target mRNA and corresponding interfering RNA and hybridizing nucleotides. The Office Action appears to acknowledge that the state of the art at the subject application's filing date was sufficiently developed such that the design of RNAi molecules for inhibiting expression of a target gene *in vitro* is a "routine technique",

requiring only "routine experimentation" (see the Examiner's stated basis for the rejection under 35 U.S.C. §103(a), set forth at page 10, lines 16-22, of the Office Action).

The written description requirement states that the applicant must describe the invention; it does not state that every invention must be described in the same way. The applicant acknowledges that sequences and structural formulas provide a convenient method of demonstrating possession of many molecules; however, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. MPEP§ 2163. In *Enzo Biochem, Inc. v. Gene-Probe, Inc.*, 63 USPQ2d 1609 (Fed Cir. 2002), the Court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed Cir. 2003), the Court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." For example, possession of an antibody may be demonstrated based on a description and characterization of its corresponding antigen. Disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and MPEP 2163 IIA3(a).

At page 5, the Office Action indicates that "the eventual identification of molecules a myriad of candidate possibilities is no substitute for the requirement of having in one's possession, at the time of filing, a representative number of species for such a broad genus claimed...". An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). There is no *per se* rule that an actual reduction to practice must occur prior to filing, or that the need to screen for candidate nucleic acid molecules precludes

adequate written description of the nucleic acid molecules. Possession may be shown in a variety of ways, including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, *e.g.*, MPEP §2163.02, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). Compliance with the written description requirement is a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 963; 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

Due to their nature, the interfering RNA and hybridizing nucleic acid molecules recited in the claims are clearly distinguishable from the compounds at issue in *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). In the latter, the Court affirmed that the description of the COX-2 enzyme did not serve to describe unknown small molecules capable of selectively inhibiting the enzyme. The teaching of the subject specification and the knowledge of the sequence and structure of the SHIP-1 gene provide one skilled in the art with a sufficient structural template and functional correlates to describe the genus of interfering RNA and hybridizing nucleic acid molecules that suppress expression of the SHIP-1 gene in human or mouse hematopoietic cells. The subject specification does not require the screening of vast amounts of candidate small molecules *de novo*, based on function alone, with no guidance provided or available as to the molecular structure of a receptor agonist to be identified. Rather, the teaching of the subject specification, the knowledge of the sequence and structure of the SHIP-1 gene, and the mechanism by which the recited molecules inhibit gene expression, together provide sufficient structural and functional correlates to demonstrate possession of the interfering RNA and hybridizing nucleotides recited in the claims. Identification of specific interfering RNA and specific hybridizing nucleotides would not just be likely, it would be inevitable and imminent. All functional descriptions of genetic

material do not necessarily fail to meet the written description requirement as a matter of law. Rather, the Court has held that the written description requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. *Enzo Biochem, Inc.* Such is the case here. The written description requirement must be considered in the context of the claimed invention and the state of knowledge in the relevant art. *Capon et al. v. Eshhar et al.*, 418 F.3d, 1349 (Fed. Cir. 2005).

The fundamental concept of the invention is that SHIP-1 deficiency would be of therapeutic benefit in suppressing transplant rejection and graft-versus-host disease (GVHD), as taught in the subject application. Furthermore, the applicant has shown that only partial SHIP-1 deficiency in the myeloid lineage is required to achieve significant suppression of allogeneic T cell responses, which mediate GVHD and graft rejection. The state of the art was sufficiently developed such that tools for inducing the required SHIP-1 deficiency were appreciated by the inventor, taught in the patent application, and available to those of ordinary skill in the art. Thus, the applicant submits that the patent application contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 38-44, 46-82, and 90-92 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully submits that the claims are fully enabled by the subject specification.

As indicated above, the Office Action appears to acknowledge that the state of the art at the subject application's filing date was sufficiently developed such that the design of RNAi molecules for inhibiting expression of a target gene *in vitro* is a "routine technique", requiring only "routine experimentation" (see page 10, lines 16-22, of the Office Action). Furthermore, at page 6, the Office Action indicates that the specification provides enablement for a method of suppressing the rejection of an allogeneic bone marrow graft from BALB/C mice in $SHIP^{-/-}$ mice or abrogating GVHD in $SHIP^{-/-}$ mice that were transplanted with whole bone marrow from BALB/C mice, thereby enhancing $SHIP^{-/-}$ mouse survival, and for the *in vivo* inhibition of SHIP-1 expression in mice using the RNAi sequences #1 and #4, and the mouse antisense vector muSHIPshRNA provided in the Declarations

by Dr. Kerr, filed July 21, 2004, and February 9, 2005. However, the Office Action indicates that the patent application does not provide enablement for inhibiting SHIP-1 *in vivo*, comprising administering any RNAi molecule specific for SHIP-1 mRNA present in mouse or human hematopoietic cells, or administering *in vivo* or *ex vivo* any nucleic acid molecule that hybridizes *in vitro* under conditions of stringency with human or mouse SHIP-1 mRNA or that hybridizes *in vivo* with SHIP-1 mRNA present in mouse or human hematopoietic cells, or suppressing transplant rejection in any patient, or treating GVHD in any patient, comprising administering any interfering RNA molecule specific for SHIP mouse or human mRNA. Specifically, the Office Action indicates that one skilled in the art would not accept the ability of co-administered RNAi molecules, or the mouse antisense vector muSHIPshRNA to target and successfully inhibit expression of the SHIP-1 gene in a mouse model, and provide an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells), as representative or correlative of the claimed subject matter,

> in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of interfering RNA in inhibiting the expression of SHIP ... following administration by any route of the claimed RNA oligonucleotides" (paragraph bridging pages 8-9 of the Office Action).

As the Examiner is aware, a specification is initially presumed to be in compliance with the enablement requirement of §112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the teachings of the patent application, coupled with information known in the art, without undue experimentation. For an Office Action to sustain a rejection on the grounds of enablement, it must provide evidence or a scientific basis for the assertion that the claimed invention could not be made or used without undue experimentation. The applicant notes that the Office Action does not state what "guidance" is missing from both the subject specification and the knowledge of those skilled in the art at the time the application was filed that is allegedly necessary to carry out the invention without resort to undue experimentation. However, it appears that the delivery of nucleic acids to cells *in vivo* with commensurate treatment effects is the main issue.

Submitted herewith are several scientific publications demonstrating successful delivery and activity of antisense oligonucleotides *in vivo* (Tong *et al.*, *Clin. Lung Cancer*, 2001, 2(3):220-226, abstract only; Lau *et al.*, *Antisense Nucleic Acid Drug Dev.*, 2002, Feb., 12(1):11-20; Prasad *et al.*, *Anticancer Res.*, 2002, Jan.-Feb., 22(1A):107-116, abstract only; Eder *et al.*, *Cancer Gene Ther.*, 2002, Feb., 9(2):117-125; Miyake *et al.*, *Clin. Cancer Res.*, 2001, 7(12):4245-4252; Choi *et al.*, *J. Clin. Invest.*, 2001, 108(12):1833-1841; Marchand *et al.*, *Am. J. Physiol. Heart Cir. Physiol.*, 2002, Jan., 282(1):H194-204; Ueta *et al.*, *Int. J. Cancer*, 2001, 94(4):545-550; Wang *et al.*, *Clin. Cancer Res.*, 2001, 7(11):3613-3624; Olson *et al.*, *Clin. Cancer Res.*, 2001, 7(11):3598-3605; Uchida *et al.*, *Mol. Urol.*, 2001, 5(2):71-78, abstract only; Tortora *et al.*, *Clin. Cancer Res.*, 2001, 7(8):2537-2544; Berg *et al.*, *J. Pharmacol. Exp. Ther.*, 2001, 298(2):477-484; Frankel *et al.*, *Cancer Res.*, 2001, 61(12):4837-4841; and Finotto *et al.*, 2001, *J. Exp. Med.*, 193(11):1247-1260).

Furthermore, the applicant submits that while the currently pending claims of the subject application are fully enabled, it is art-recognized that RNAi differs from antisense-mediated interference in both approach and effectiveness. Antisense-mediated genetic interference requires delivery to a cell interior of specific-single-stranded nucleic acid molecules at a concentration that is equal to or greater than the concentration of endogenous mRNA. RNAi has advantages over antisense both in the stability of the material to be delivered and the concentration required for effective inhibition (see page 2, lines 12-29, and page 4, lines 14-25, of International Publication WO 99/32619 (Fire *et al.*). Furthermore, compared to antisense or ribozyme technology, the secondary structure of the target mRNA does not appear to have a strong effect on RNAi-mediated silencing (see Harborth J. *et al.*, *J. Cell Sci.*, 2001, Dec., 114 (Pt. 24):4557-4565). In fact, RNAi has now become such a popular tool for gene silencing, many companies use proprietary algorithms to design and chemically synthesize siRNAs using a conventional DNA/RNA synthesizer. Research groups have created human shRNA libraries that target thousands of genes and used them to identify new genes (see pages 80-81 and 84 of Bonetta, L. "RNAi: Silencing never sounded better" *Nature Methods*, 2004, 1(1):79-86).

The use of gene delivery vehicles, such as vectors, for administration of SHIP-1 inhibitory substances, were contemplated at the time of filing and disclosed at page 11, lines 19-25, and page 12 of the specification.

> The delivery vehicle can be any component or vehicle capable of accomplishing the delivery of a gene or a substance to a cell, for example, a liposome, a particle, naked DNA, or a vector. A gene delivery vehicle is a recombinant vehicle, such as a recombinant viral vector, a nucleic acid vector (such as plasmid), a naked nucleic acid molecule such as a gene, a nucleic acid molecule complexed to a polycationic molecule capable of neutralizing the negative charge on the nucleic acid molecule and condensing the nucleic acid molecule into a compact molecule, a nucleic acid associated with a liposome (Wang, *et al.*, *PNAS* 84:7851, 1987), and certain eukaryotic cells such as a producer cell, that are capable of delivering a nucleic acid molecule having one or more desirable properties to host cells in an organism. The desirable properties include the ability to express a desired substance, such as a protein, enzyme, or antibody, and/or the ability to provide a biological activity, which is where the nucleic acid molecule carried by the gene delivery vehicle is itself the active agent without requiring the expression of a desired substance (page 11, line 34; and page 12, lines 1-13, emphasis added).
>
> One example of such biological activity is gene therapy where the delivered nucleic acid molecule incorporates into a specified gene so as to inactivate the gene and "turn off" the product the gene was making, or to alter the translation or stability of the mRNA of the specified gene product. Gene delivery vehicle refers to an assembly which is capable of directing expression of the sequence(s) or gene(s) of interest or of turning off the gene of interest (page 12, lines 13-18).

Hairpin expression vectors have been used for delivery of RNAi to mammalian cells, as demonstrated by Yu *et al.* (*PNAS*, 2002, Apr., 99(9):6047-6052), Paddison *et al.* (*PNAS*, 2002, Feb., 99(3):1443-1448); Abbas-Terki *et al.*, *Hum. Gene Ther.*, 2002, Dec., 13(18):2197-2201); Svoboda *et al.*, *Biochem. Biophys Res. Commun.*, 2001, 287(5):1099-1104); and Ma *et al.* (*Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi*, 2002, Sept., 16(3):253-355, abstract only), which are submitted herewith. Cationic liposomes such as DOTAP are positively charged and interact with the negatively charged DNA molecules to form a stable positively charged DNA/liposome complex, which is internalized by the cell. Cationic lipids such as DOTAP have been used as nucleic acid delivery vehicles for some time (see, for example, column 17 of U.S. Patent No. 6,025,198, Bennett *et al.*, "Antisense Modulation of SHIP-2 Expression", of record; Porteous *et al.*, "Evidence for safety and efficacy of DOTAP cationic liposome mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis", *Gene Ther.*, 1997, 4(3):210-218, submitted herewith; Song *et al.*, "Characterization of cationic liposome-mediated gene transfer *in vivo* by intravenous administration", *Hum. Gene Ther.*, 1997, 8(13):1585-1594, abstract only, submitted herewith; and

Ott *et al.*, "A cationic sub-micron emulsion (MF59/DOTAP) is an effective delivery system for DNA vaccines," *J. Controlled Release*, 2002, 79:1-5, submitted herewith).

Consideration is to be given to post-filing date evidence (*e.g.*, Declarations and Exhibits) offered by the applicant to show that the claimed invention works, provided that the evidence is consonant with the teachings of the specification as filed. In making this determination, the Examiner is to compare the materials and methods used in the experiments of the Declaration and Exhibits with those taught in the application to make sure that they are commensurate in scope. This means that the Examiner is to confirm that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art (MPEP §2164.05). Thus, the requirement of consonance between the submitted evidence and the teachings of the specification is not evaluated in a vacuum. Rather, the determination is to be made from the standpoint of one of ordinary skill in the art. The applicant respectfully submits that the Examiner is giving no credit (*i.e.*, according no knowledge) to those persons of ordinary skill in the pertinent art of nucleic acid delivery, for example. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass,* 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). As iterated in MPEP 608.01(p), the prior art setting may be mentioned in general terms. It is "the essential novelty, the essence of the invention, [that] must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

The enablement requirement of 35 U.S.C. §112, first paragraph, does not require that the applicant reinvent the wheel. There is no need to inform the layman nor disclose what one of ordinary skill in the art already possesses.

> Paragraph 1 permits resort to material outside of the specification in order to satisfy the enablement portion of the statute because it makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention. One skilled in the art knows how to make and use a bolt, a wheel, a gear, a transistor, or a known chemical starting material. The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel. *Amtel Corporation v. Information Storage Devices, Inc.*, 198 F.3d 1374; 53 USPQ2d 1225 (Fed. Cir. 1999).

In initial RNA interference studies, many researchers opted to combine multiple small interfering RNAs (siRNAs) that targeted distinct regions of the same gene to facilitate degradation of the target mRNA (see page 214, second paragraph, lines 23-38, of Zou and Yoder, *Biol. Cell*, 2005, 97:211-219, which is submitted herewith). The desire to mix siRNAs arose primarily from the finding that not every randomly-designed siRNA significantly reduced target gene expression. The pooling strategy increased the chances of reducing target gene expression of random-designed siRNAs. Therefore, this is a technique to increase efficiency, avoiding the necessity to test each candidate siRNA individually. While there have been reports of more robust knockdown of target gene products using a pool of siRNA compared with a single siRNA, there is no reason to believe that administration of a pool of siRNA would be required to reduce SHIP-1 expression sufficiently to obtain a therapeutic benefit (*e.g.*, suppression of graft rejection or GVHD). As the Examiner is aware, the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re wands*, 858 F.2D 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). MPEP §2164.06. "Tedious and laborious" experimentation is not necessarily undue experimentation for purposes of enablement under 35 U.S.C. §112, first paragraph. *Ex parte Erlich* 3 USPQ2d 1011 (BPAI 1982).

The SHIP-1 knockout models utilized in the Examples of the subject application and Dr. Kerr's Declarations demonstrate that SHIP-1 deficiency results in a phenotype that is of therapeutic benefit, and that this phenotype is achieved in the absence of complete SHIP-1 silencing. The evidence of record shows that nucleic acid molecules, such as interfering RNA, can be successfully

delivered to cells *in vitro* and *in vivo*, and achieve the required level of SHIP-1 knockdown established with the SHIP-1 knockout models.

The applicant previously submitted the unpublished Paraiso *et al.* manuscript entitled "Induction of SHIP deficiency prior to allogeneic bone marrow transplant enhances engraftment and survival", of which Dr. Kerr is a co-author. The manuscript demonstrates that induction of SHIP-deficiency in the adult allogeneic bone marrow transplant recipient enhances both the quality and duration of their post-transplant survival. When taken with the other experimental evidence submitted with the applicant's previous responses, it is clear that: (1) SHIP deficiency can be induced just prior to engraftment and still result in enhanced transplant survival; (2) even partial SHIP deficiency will enhance transplant survival; and (3) nucleic acid molecules, such as interfering RNA can be administered to a human or mouse recipient using known delivery methods to achieve the required SHIP deficiency, without resort to undue experimentation.

The applicant respectfully submits that, in view of the state of the art of nucleic acid delivery at the time the application was filed, one of ordinary skill in the art would be able to make and deliver agents, such as interfering RNA, to human cells *in vitro* and *in vivo*, without the need for undue experimentation. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 67-73 have been rejected under 35 U.S.C. §103(a) as being obvious over Damen *et al.* (*Proc. Natl. Acad. Sci. USA*, 1996, 93:1689-1693) and Ware *et al.* (*Blood*, 1996, 88:2833-2840) in view of Fire (U.S. Patent No. 6,506,559) and Gill *et al.* (U.S. Patent No. 5,804,412). The applicant respectfully submits that the claims are not obvious over the cited references. However, by this Amendment, claims 67-73 have been cancelled, rendering this rejection moot.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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GPL/mv

Attachments: Request for Continued Examination
Supplemental Information Disclosure Statement, Form PTO/SB/08, references
Tong *et al.*
Lau *et al.*
Prasad *et al.*
Eder *et al.*
Miyake *et al.*
Choi *et al.*
Marchand *et al.*
Ueta *et al.*
Wang *et al.*
Olson *et al.*
Uchida *et al.*
Tortora *et al.*
Berg *et al.*
Frankel *et al.*
Finotto *et al.*
Yu *et al.*
Paddison *et al.*
Abbas-Terki *et al.*
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Zou and Yoder